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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/673,254 | 12/06/2000 | Augusto Inventi Solari | P101615 -0000 | 8796 |

7590 03/07/2003

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| EXAMINER | |
|---|---|
| MOORE, WILLIAM W | |
| ART UNIT | PAPER NUMBER |
| 1652 | |

DATE MAILED: 03/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/673,254 | Applicant(s) SOLARI ET AL. | |
|---|---|---|---|
| | Examiner William W. Moore | Art Unit 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 10-12, and 14-19* is/are rejected.

7)☒ Claim(s) *9 and 13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Bibliographic Data Sheet* .

## DETAILED ACTION

### *Priority*

While Amendment B, Paper No. 13 filed December 20, 2002, amends page 1, line 1, of the specification to claim the benefit of an earlier filing date under 35 U.S.C. §120, it is noted that the International Application described in the amendment is itself based on U.S. application serial No. 09/065,606 filed April 24, 1998, and now abandoned. This relationship is set forth in the Declaration of Inventorship filed with the instant Application and USPTO records also indicate that the named International Application represents a continuation of application serial No. 09/065,606. It is suggested that Applicant may wish to determine whether further amendment of page 1 of the specification is advisable. Applicant may also wish to request a Corrected Filing Report in view of the information set forth in a copy of the most recent USPTO bibliographic data attached hereto, wherein one of the names of the co-inventors is absent.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(e), (f) or (g) prior art under 35 U.S.C. §103(a).

Claims 1-5, 7, 8, 10-12 and 14-19 are rejected for reasons of record under 35 U.S.C. §103(a) as being unpatentable over either of Inventi et al., U.S. 5,695,966, or Dickens et al., 1996, and Stassi et al., WO 97/06266, in view of any among Hwang et al., Kaur, or Caruso et al., WO 89/11532.

Applicant's arguments filed December 20, 2002, have been fully considered but they are persuasive only with regard to claim 9, no longer subject to this rejection. Applicant does not dispute that the prior art teaches (1) that increased doxorubicin levels in the medium of a host cell results in increased toxicity to the host cell and (2) that such toxicity can be relieved by transforming the host cells with DNA molecules encoding either or both of the *drr*A and *drr*B doxorubicin resistance genes in order either to augment doxorubicin resistance where the cell exhibits some native doxorubicin resistance, or to confer the phenotype of resistance where the cell has none. Applicant generally suggests at pages 2-5 of Paper No. 12 that each individual reference must contain a teaching or suggestion pointing directly to an advantage taught in another reference that is otherwise apparent to one of ordinary skill in the art. Applicant's general argument ignores the fact that the efforts of each of the groups of scientists who published the teachings upon which this rejection is based recognized the importance of producing anthracycline antibiotics such as daunorubicin and doxorubicin in transformed microbial host cells since these antibiotics are used in anti-cancer chemotherapy. Applicant's approach is represented by a suggestion at page 2 of Paper No. 12 that it is improper to combine the teachings of Hwang et al. with teachings of Inventi et al., Dickens et al., or Stassi et al. because Hwang et al. discuss, at page 1618, recombinant expression of a *dnr*F gene in *Streptomyces* transformants using their pCM213 plasmid. Applicant's suggestion speciously ignores the teachings at page 1617 of Hwang et al. (1) that transformants expressing genes conferring doxorubicin resistance, the *drr*A and the *drr*B genes present in both plasmids pCM1 and pCM4, are better protected from both daunorubicin and doxorubicin - demonstrated by the results in Table 1 at page 1618 - and (2) that joint *drr*A and *drr*B expression will, "confer significantly higher levels of resistance to [doxorubicin] by comparison with those for [daunorubicin]", page 1617, right column. Hwang et al. then explain the basis for this

resistance by teaching, id., that that the two genes encode products similar to a mammalian "multidrug resistance protein [ ] which mediates the outward transport of such anticancer drugs as doxorubicin". Hwang et al. show, Table 1, page 1618, that *S. lividans* and *S. galilaeus* microbial host cells which have no genes corresponding to the *S. peucetius* *drr*A and *drr*B genes, are resistant to 6- to 10-fold increased concentrations of doxorubicin and resistant as well to 8- to 15-fold increased concentrations of doxorubicin when transformed with plasmids pCM1 and pCM4, wherein both plasmids permit recombinant expression of both genes, by comparison with cells transformed with a plasmid that does not comprise these genes or cells that are not transformed with a plasmid. The pCM1 plasmid further comprises, see Figure 2 at page 1617, the *dnr*F gene encoding an active DnfR hydroxylase – the straw man of Applicant's argument – while the pCM4 plasmid has an incomplete *dnf*R gene and cannot express an active hydroxylase, but Table 1 shows that the presence or absence of this further gene has no influence on the doxorubicin resistance conferred by the *drr*A and *drr*B genes and little influence on the daunorubicin resistance conferred by the *drr*A and *drr*B genes. One of ordinary skill in the art would not have considered that the teachings of Hwang et al. concerning the activity of the *dnf*R gene product to be inseparably linked to teachings of Hwang et al. of the resistance conferred by *drr*A and *drr*B genes, particularly where Figure 2 and Table 1 of Hwang et al. show that the separate characteristics of the encoded products of the three genes are not, and need not be, linked.

Kaur and Caruso et al. amplify and confirm the teachings of Hwang et al. where Kaur verifies the functions for the *drr*A and *drr*B gene products predicted by Hwang et al. and where Caruso et al. specifically teach, see claims 11-16, that doxorubicin resistance genes should be placed in a plasmid comprising a promoter that will drive their expression and that the plasmid should be used to transform a microbial host cell that produces

doxorubicin in order to improve its doxorubicin production. Applicant offers no reason why one of ordinary skill in the art would have failed to read the teachings of Hwang et al., Kaur, and Caruso et al. broadly, and would have instead adopted the narrow, specious, reasoning that Applicant advances. Where an Applicant fails to point "to any of evidence of record indicating that the findings of [fact in made in a rejection under 35 U.S.C. §103(a)] on [a motivation] issue are unsupportable" a legal finding of obviousness based on those facts may be sustained. *In re Berg*, 02-1120, 02-1160 (Fed. Cir. 2003).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include the *drr*A and *drr*B doxorubicin resistance genes taught by Hwang et al. in preparing expression plasmids – DNA molecules – comprising a *dox*A gene encoding a C-14 hydroxylase that Inventi et al. and Dickens et al. teach is useful in transforming microbial cells, Examples 1 and 2 of Inventi et al. and pages 3391-3394 of Dickens et al., where the *dox*A gene is linked to a strong plasmid promoter, in order to conduct a recombinant process for producing doxorubicin. This is because such an artisan, aware of the nature of *drr*A and *drr*B doxorubicin resistance taught by Hwang et al. which is amply demonstrated in Table 1 of Hwang et al. by host cells transformed with both *drr*A and *drr*B doxorubicin resistance genes, would reasonably expect that including these genes in a plasmid DNA molecule comprising a cloned *dox*A gene of Inventi et al. or Dickens et al. would improve the recombinant production of the toxic product, doxorubicin, by such host cells where both Inventi et al. and Dickens et al. teach that their *dox*A genes encode a polyketide hydroxylase that converts daunorubicin to doxorubicin, where Inventi et al. particularly teach, Figure 1, the 2.9kb *Bam*HI-*Sph*I restriction endonuclease segment comprising an internal 1269-nucleotide sequence encoding a DoxA product required by claims 7 and 8 herein and where Dickens et al. teach an a 1269-nucleotide sequence

encoding a DoxA product nearly identical in amino acid sequence to the DoxA product of Inventi et al.

Applicant next argues limitations not present in the claims at page 3 of Paper No. 12, where no pending claim requires either Applicant's specific vector construct or any specific degree of bioconversion efficiency, and at page 4 of Paper No. 12, where no pending claim requires that any resistance gene be replaced by another and where no pending claim requires that a vector comprise the *dnr*V and Δ*dnr*U fragments Applicant mentions. The argument at page 5 of Paper No. 12 that the prior art teachings relied on herein fail to meet all limitations of the claims is inappropriate where the only limitations to which Applicant can point are absent from the claims.

While Applicant concedes at pages 3 and 4 of Paper No. 12 that the *erm*E* promoter is "well-known" in the art, Applicant separately argues that one of ordinary skill in the art at the time the invention was made would have had no motivation to use this strong and constitutive promoter, frequently used by many microbiologists since its development in 1992,[1] in an expression plasmid of claims 1-3 because Stassi et al. had used the promoter in an expression plasmid to promote the high level expression of a *S. erythraea* polyketide hydroxylase in a *Saccharopolyspora erythraea* host cell for the recombinant production of an erythromycin derivative. Yet Stassi et al. teach, page 5, lines 5-8, that their process may be practiced in *Streptomyces* host cells and specifically used the promoter to drive high level expression of a polyketide hydroxylase gene. Applicant fails to indicate why one of ordinary skill in the art, aware of the *erm*E* promoter's characteristics which make it a frequent choice of artisans in preparing plasmids for use in recombinant methods of making desired gene products in streptomycete host cells would not have considered it

[1] See, e.g., Pierpersberg et al., U.S. Patent No. 5,656,453, Denoya, U.S. Patent No. 5,728,561, and Friedmann et al., U.S. Patent No. 5,728,561, all made of record herewith.

advantageous to substitute the *erm*E* promoter for (a) native promoter(s) of either or all of the *dox*A gene, *drr*A gene and *drr*B gene, particularly where none of these genes' native promoters are either strong or constitutive. The rejection of record of claims 1-5, 7, 8, 10-12 and 14-19 is therefore sustained.

Claim 6 is rejected for reasons of record under 35 U.S.C. §103(a) as being unpatentable over Inventi et al. or Dickens et al., Stassi et al., and any of Hwang et al., Kaur, or Caruso et al. as applied to claims 1-5, 7, 8, 10-12 and 14-19 above, and further in view of Lomovskaya et al.

Applicant's arguments filed December 20, 2002, have been fully considered but they are persuasive only with respect to claim 13, no longer subject to this rejection. Applicant suggests at pages 5-6 of Paper No. 12 that doxorubicin-producing transformants of Inventi et al. "can be [daunorubicin] or [doxorubicin] sensitive", but that the transformants also, contrarily, "possess another mechanism that confers [daunorubicin] sensitivity or removes [doxorubicin] sensitivity from the host cells". This suggested interpretation of teachings of Inventi et al., were it accurate, could not teach away from, or discourage, one of ordinary skill in the art at the time the invention was made desiring to improve the doxorubicin resistance of a cell transformed with a gene, such as the *dox*A gene of Inventi et al., that causes it produce more doxorubicin. It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a DNA molecule comprising the *dox*A gene of Inventi et al. and to further include the *drr*C gene taught by Lomovskaya et al. to confer resistance to doxorubicin together with the *drr*A and *drr*B genes taught by Hwang et al. to confer resistance to doxorubicin, in order to transform *Streptomyces* host cells with the resulting plasmid expression vector – which would be a DNA molecule according to claim 6 herein – in order to conduct the doxorubicin biosynthetic processes of claims 18 and 19 herein. This is because the prior art in general teaches that increasing production of doxorubicin in a host cell results in increased toxicity to the host cell by the product and that such toxicity can be relieved by instituting or augmenting doxorubicin

resistance by conferring doxorubicin resistance, a phenotype that can be conveyed by transforming the host cells with plasmids expressing a *drr*C doxorubicin resistance gene. The rejection of record is therefore sustained.

*Conclusion*

Claims 9 and 13 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims because they are free of the prior art of record which fails to teach the specific restriction endonuclease cleavage sites required by claim 9 and fails to teach the specific characteristics of the plasmids of claim 13.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached between 9:00AM-5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached at 703.308.3804. Further fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. The examiner's direct FAX telephone number is 703.746.3169. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

William W. Moore
March 4, 2003

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